PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PP20407003	**FOR FURTHER ACTION** see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US04/12510	International filing date (*day/month/year*) 23 April 2004 (23.04.2004)	(Earliest) Priority Date (*day/month/year*) 25 April 2003 (25.04.2003)
Applicant CHIRON CORPORATION		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the Report**
   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      ☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.
2. ☐ **Certain claims were found unsearchable** (See Box No. II)
3. ☐ **Unity of invention is lacking** (See Box No. III)
4. With regard to the **title**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      ☐ as suggested by the applicant.
      ☐ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☒ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/12510

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:

   a. type of material

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material

   ☐ in written format

   ☒ in computer readable form

   c. time of filing/furnishing

   ☐ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☒ furnished subsequently to this Authority for the purposes of search

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/12510

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07H 21/04; C12N 15/00
US CL : 536/23.72; 435/320.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 536/23.72, 24.1; 435/320.1; 424/184.1, 192.1, 450, 228.1, 278.1, 283.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
West, PubMed

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01/47551 A (CHIRON CORPORATION) 05 July 2001 (05.07.2001), document.	1-29
Y	WO 03/002065 A (CHIRON CORPORATION) 09 January 2003 (09.01.2003), document, esp., Fig. 2, and claims.	1-29
Y	US 6,210,663 B (ERTL, Hildegund) 03 April 2001 (03.04.2001), abstract, columns 2-3, 10-14.	12-28
A	US 2003/0072764 A (O'HAGAN, Derek) 17 April 2003 (17.04.2003), reference.	1-29
A	US 6,086,901 A (O'HAGAN et al) 11 July 2000 (11.07.2000), reference.	17-20, 22-26
A	WO 02/26209 A (CHIRON CORPORATION) 04 April 2002 (04.04.2002), reference	3-6, 9-11, 22-27
A	US 6,207,646 B (KRIEG et al) 27 March 2001 (27.03.2001), reference.	21, 27

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
01 April 2005 (01.04.2005)

Date of mailing of the international search report
15 APR 2005

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer
Zachariah Lucas

Telephone No. 571-272-1600

Form PCT/ISA/210 (second sheet) (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
ALISA HARBIN
CHIRON CORPORATION
INTELLECTUAL PROPERTY - R440
P. O. BOX 8097
EMERYVILLE, CA 94662-8097

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*)	15 APR 2005
Applicant's or agent's file reference PP20407003	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US04/12510	23 April 2004 (23.04.2004)	25 April 2003 (25.04.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): C07H 21/04; C12N 15/00 and US Cl.: 536/23.72; 435/320.1

Applicant

CHIRON CORPORATION

1. This opinion contains indications relating to the following items:

- [X] Box No. I — Basis of the opinion
- [ ] Box No. II — Priority
- [ ] Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV — Lack of unity of invention
- [X] Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI — Certain documents cited
- [ ] Box No. VII — Certain defects in the international application
- [ ] Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis(b)* that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Zachariah Lucas Telephone No. 571-272-1600

Form PCT/ISA/237 (cover sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/12510

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☒ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☒ in computer readable form

c. time of filing/furnishing

☐ contained in international application as filed.

☐ filed together with the international application in computer readable form.

☒ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/12510

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-29	YES
	Claims NONE	NO
Inventive step (IS)	Claims NONE	YES
	Claims 1-29	NO
Industrial applicability (IA)	Claims 1-29	YES
	Claims NONE	NO

2. Citations and explanations:

Claims 1-11, 28, and 29 lack an inventive step under PCT Article 33(3) as being obvious over WO 01/47551 in view of WO 03/02065. These claims are directed to immunogenic compositions comprising a polynucleotide encoding an HCV E1E2 complex, and methods of using or making such. The claims further required that the E1E2 proteins of the complex comprise a sequence at least 80% identical to that disclosed in positions 192-809 of Figures 2A-2C of the present application (the numbers indicating the position of the residues in the full length HCV polyprotein- see page 9).

WO 01/47551 teaches a method of inducing an anti-HCV immune response comprising the administration of a polynucleotide encoding and HCV E1E2 complex. Abstract. Among the effective antigens for the polynucleotide to encode, the reference refers to residues 192-809 of the HCV polyprotein. The reference teaches that the polynucleotide to be administered may include control sequences to direct the expression of the administered sequence. Pages 10-11. Further, the reference also teaches that the polynucleotide may be administered in a form where it is adsorbed to a microparticle composed of a polymer such as poly(D,L-lactide-co-glycolide). Page 22. However, while the reference indicates that any HCV sequence may be used (page 17), the reference does not specify a sequence falling within the scope of the present claims.

The WO03/02065 reference does however provide an E1E2 sequence that falls within the scope of the present claims. The reference additionally teaches that the sequence is an effective HCV antigen. It would therefore have been obvious to those in the art to use a polynucleotide encoding this sequence in the method disclosed by WO 01/47551. The combined teachings of these references therefore render the claims obvious.

Claims 12-27 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the immediately preceding paragraph and further in view of Ertl et al. (Us 6,210,663). These claims describe the methods as indicated above, except that they additionally require the subsequent administration of a boosting vaccine comprising the protein form of the E1E2 complex encoded by the previously administered polynucleotide.

The teachings of the two WO references have been described above. While the references together teach the method of claim 1, the references do not teach or suggest the later administration of a protein antigen composition, wherein the protein antigen is that encoded by the polynucleotide, subsequent to the administration of the polynucleotide. However, the Ertl reference does provide such teachings. See e.g., abstract, columns 12-13. In view of these teachings, and the teaching in the WO 03/002065 reference indicating that the E1E2 complex is an effective anti-HCV antigen, it would have been obvious to combine the teachings of Ertl with the WO document to arrive at the claimed methods.

Certain of the indicated claims also indicate that the boosting composition may comprise an adjuvant, either in the form of a submicron oil-in-water emulsion, or a CpG. In addition to the teachings described above, Ertl also teaches that the boosting composition may comprise an adjuvant. Column 13, lines 54-58. The WO03/02065 reference provides examples of adjuvants that may be effectively used with the indicated E1E2 antigen, including the adjuvants described in the present claims. See e.g., claims 5, 24-30 of the WO03/02065 reference.

The combined teachings of these references therefore render the claimed compositions and methods obvious.